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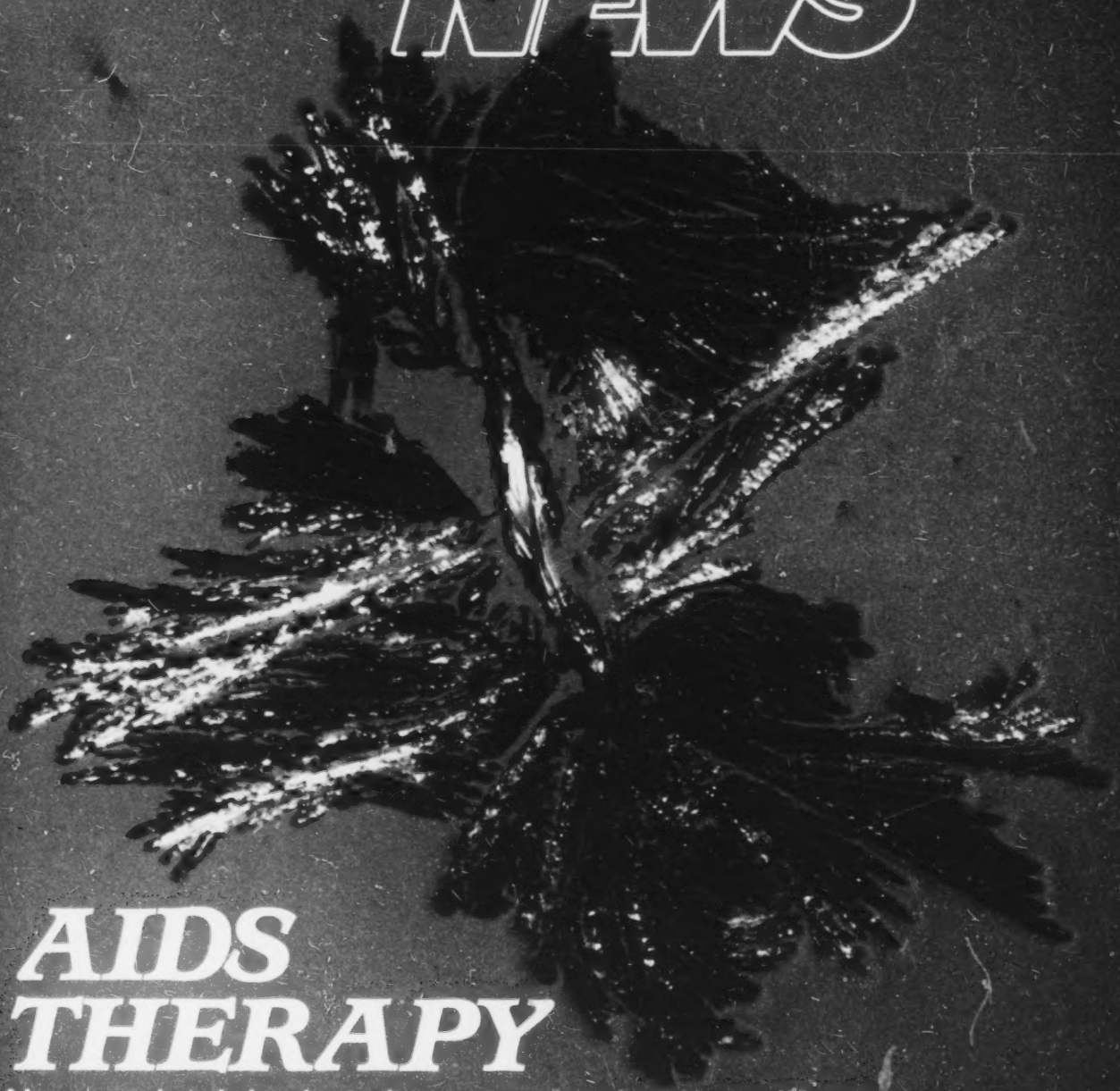
DECEMBER 8, 1986

CHEMICAL & ENGINEERING

NEWS

1987 Pittsburgh Conference Program
Page 34



AIDS THERAPY

No cure in sight, but drug, vaccine leads proliferate
Page 7

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CHEMICAL & ENGINEERING NEWS

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News of the Week

■ **Unilever seeks to acquire Chesebrough-Pond's, as chemical merger activity heats up before tax reform law takes effect.** **Page 4**

■ **William Graham, new Presidential science adviser, outlines prevailing themes in the Office of Science & Technology Policy.** **Page 4**

■ **Low-cost, easy-to-use kit for drug screening is now available from Keystone Medical Corp.** **Page 5**

■ **Finnish chemicals producer Kemira buys Belgian nitrogen and fertilizer operations in attempt to boost its output, particularly in European Economic Community countries.** **Page 5**

■ **Allegedly falsified research data published in *JACS* is withdrawn by noted organic chemist Ronald Breslow.** **Page 6**

■ **In the Bhopal case, Indian court frees Union Carbide's assets, thus enabling Carbide to proceed with its reorganization and recapitalization plans.** **Page 6**

Cover: Crystal of azidothymidine, a promising anti-AIDS drug, photographed in polarized light, magnified 25 times. Copyright Will and Deni McIntyre

Letters 2

Concentrates

Business 17
Government 25
Science/Technology 28

The Departments

New Products 46
Newscripts 62

Business

Third-quarter earnings at major pharmaceutical firms continue the strong advances of second-quarter 1986. **Page 22**

Government

U.S. drug companies' problems in the world marketplace include lack of patent protection in many countries, political implications of World Health Organization's guidelines on pharmaceuticals. **Page 26**

Science

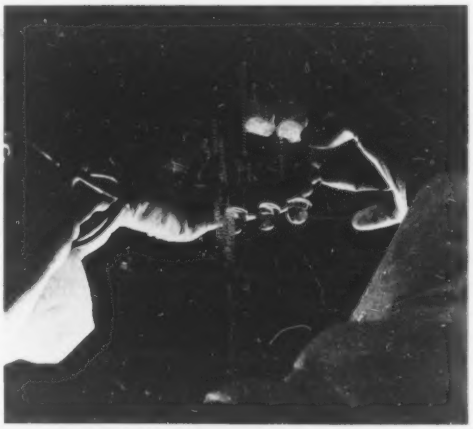
Use of fredericamycin A in cancer therapy may be closer: Its parent compound has been synthesized and there is evidence that free radical formation may be a key to its anticancer activity. **Page 30**

Technology

Silicone heat-transfer fluids are taking a larger share of the market because of their wide useful temperature range. **Page 32**

Meetings

1987 Pittsburgh Conference miniprogram includes symposium sessions, registration and other information. **Page 34**



News Focus

The quest for drugs to treat AIDS and a vaccine to prevent it is intensifying and taking many different directions. **Page 7**

Efforts Intensify To Develop Drugs, Vaccines that Combat AIDS

Dozens of potential treatments are in clinical and preclinical study, and a variety of strategies are being explored to protect healthy people from the virus that causes AIDS

Ron Dagani, C&EN Washington

This is the second of a two-part series on the AIDS crisis. Last week C&EN published an article outlining the progress researchers have made in elucidating the nature, behavior, and biological effects of the AIDS virus (Dec. 1, page 7). This concluding article deals with efforts to develop drugs to treat AIDS and vaccines to prevent it.

Scientist does antiviral research at Burroughs Wellcome Co., maker of AZT

Seven years ago few had ever heard of acquired immune deficiency syndrome, or AIDS. This puzzling affliction, then seen in only a small number of young, homosexual men, was something new and unnamed. Today, it's hard to find anyone in the U.S. who hasn't heard of AIDS, the disease that can debilitate and then kill its victim with horrific swiftness.

AIDS has come to be recognized as a public health emergency. More than 27,700 American men, women, and children have been stricken by it; the death toll is 16,000 and rising. The U.S. Public Health Service predicts that by the end of 1991 more than 179,000 persons will have succumbed to the disease.

So far, there is no cure—not even a satisfactory treatment—for AIDS. And a vaccine, if it's possible to develop one at all, won't be available for at least five years.

Nonetheless, the fear, despair, and helplessness surrounding the disease are just beginning to be counterbalanced by a measure of hope. At research centers and hospitals around the world, scientists and physicians are engaged in a frantic search for drugs and vaccines to stem the growing epidemic. One drug—azidothymidine (AZT)—has already shown some benefits in AIDS patients. And dozens of other potential treatments are in various stages of clinical and preclinical study. In addition, a variety of vaccine strategies are being explored to protect healthy people from the virus that causes AIDS. Many researchers seem optimistic that progress will be made, albeit slowly.

Medical researchers face a most formidable—and unique—enemy. AIDS is the first infectious disease in history that specifically targets the body's immune system. Once it has crippled that complex network of defenses, a host of other pathogens can invade the body and run wild, causing so-called opportunistic infections. Those infections are what make AIDS fatal. Thus, scientists have been handed an unprecedented triple challenge: Stop the AIDS virus, restore the dam-

A selection of experimental anti-AIDS drugs at a glance

AL 721. Lipid mixture composed of neutral glycerides, phosphatidylcholine, and phosphatidylethanolamine in 7:2:1 ratio. Interferes with HIV infectivity but not by inhibiting reverse transcriptase; possibly it disrupts the virus's membrane. No adverse effects observed during a six-week clinical trial.

Ampligen. Mismatched double-stranded RNA polynucleotide that induces the body to release interferon, thus stimulating antiviral activity. Reportedly does not have side effects of interferon injections. Currently undergoing preliminary clinical trials in AIDS patients.

Ansamycin (rifabutin, $C_{45}H_{29}N_4O_{11}$). Italian antibacterial drug, a member of the rifamycin group of antibiotics, which are characterized by a natural ansa structure (chromophoric naphthohydroquinone group spanned by a long aliphatic bridge). Drug has shown some efficacy in treating AIDS patients with an opportunistic infection caused by the bacterium *Mycobacterium avium-intracellulare*.

Azidothymidine (AZT, 3′-azido-3′-deoxythymidine). First drug to show promise in prolonging lives of patients with AIDS or AIDS-related complex (ARC). Well absorbed orally and effectively penetrates central nervous system, but has relatively short half-life in the body and some toxicity, with anemia and headaches. ARC patients treated with AZT showed virtually no toxic effects.

Azimexon. Cyanaziridinyl immune modulator. Early trial showed improvements in symptoms and immune function in patients with ARC but not AIDS; only toxic effect was mild hemolysis (disintegration of red blood cells with release of hemoglobin), which disappeared when treatment ceased.

Cyclosporine (cyclosporin A). Cyclic oligopeptide with potent immunosuppressive effects, used in cancer therapy. Inhibits T4 lymphocyte-dependent immune responses. Basis of controversial AIDS therapy in France; rationale is that HIV infects "activated" T4 cells, which are primed to defend that body, so drug that prevents activation of T4 cells may limit progression of disease. The French claim encouraging results with it.

Foscarnet (trisodium phosphonoformate). Swedish drug that has been used to treat CMV infection in immunocompromised patients, also to treat herpes. Inhibits HIV reverse transcriptase activity in vitro at levels pharmacologically acceptable in vivo. Formulation problems and serious side effects have been encountered. No results yet reported in HIV-infected patients.

HPA-23 (ammonium 21-tungsto-9-antimoniate, $[(NH_4)_{18}(NaW_{21}Sb_9O_{86})_{17}]$. Used to treat actor Rock Hudson in Paris. Inhibits reverse transcriptase in

aged immune system, and treat the opportunistic infection.

No one believes a single "magic bullet" will do it all. Immunologist Matthew F. Heil thinks therapy for AIDS patients likely will consist of "a successive series of stopgap measures"—drugs to stop the virus from reproducing, drugs to boost the immune response, and drugs to treat the opportunistic infections. Step by step, scientists will slowly learn how to extend the life span of AIDS patients, says Heil, a consultant to the biotechnology industry. "It's not going to happen all at once," he cautions.

An important first step, though, has already been taken. In a recent study, AIDS patients given the antiviral drug AZT resisted opportunistic infections better and remained alive in greater numbers than patients given a placebo (C&EN, Sept. 29, page 6). The survival disparity between the two groups of patients became so dramatic that the trial was halted prematurely so the placebo group could be switched to AZT therapy. Most of those patients are still receiving the drug, and scientists are anxiously waiting to see how long it will keep them alive.

In the meantime, new clinical trials of AZT have begun, including one that involves children with AIDS. And Burroughs Wellcome Co., the North Carolina firm that manufactures the drug, is now offering it to thousands of additional AIDS sufferers. Early in 1987, the Food & Drug Administration is expected to give the company the nod to market the drug.

Although AZT has given certain AIDS patients new hope, it probably won't be the ultimate weapon against the disease. The drug has a number of drawbacks, the chief one being that it suppresses production of the body's bone marrow cells. Such a side effect could not be tolerated for the long period of time—perhaps a lifetime—that the patient might have to take the drug.

The international search for therapeutic agents against AIDS is only beginning, and as a result, it appears to be in some disarray. Basically, researchers are trying almost anything that looks like it might be able to stop human immunodeficiency virus (HIV), the retrovirus that causes AIDS, in its tracks. Some of the candidate drugs being tested, such as ansamycin and ribavirin, are established drugs for other ailments. Other candidates, such as AZT and its chemical cousins, have emerged from ambitious drug-screening programs. The National Cancer Institute, for instance, has a repository of more than 500,000 medicinal compounds that it is screening for activity against HIV.

Scientists also are trying to design new anti-AIDS drugs from scratch. The National Institutes of Health is making a major effort in this direction. Leading the initiative are the National Institute of Allergy & Infectious Diseases (NIAID) and NCI, which together are funneling $11.5 million this fiscal year to researchers through five cooperative drug-discovery groups.

Some of the new drug-discovery initiatives are aimed at blocking various stages in the life cycle of the AIDS virus. To reproduce, the virus must bind to a host cell, enter it, and then shed its viral coat, freeing its RNA genome. Using its own reverse transcriptase, the virus makes a double-stranded DNA copy of its genome. The copy is integrated into the host cell's chromo-

several retroviruses in vitro, but mechanism of antiviral action against HIV is unknown. Drug has shown some tendency to check the growth of HIV, but no therapeutic benefit has been documented in AIDS patients.

Imreg-1. Proprietary immune modulator derived from white blood cells. Reportedly can enhance production of other biological response modifiers such as interleukin-2 and γ-interferon, which are critical to normal functioning of immune system.

Inosine pranobex (isoprinosine, inosiplex). *p*-Acetamidobenzoic acid salt of dimethylaminoisopropanol:inosinate complex (3:1 molar ratio). Chemically synthesized antiviral and immune modulator originally developed to enhance memory in elderly. In one study, found to improve immune function in ARC patients.

α-Interferon. Glycoprotein produced by cells in response to virus infection; helps amplify or regulate immune responses. Checks the growth of HIV in vitro. Has induced tumor regression in some AIDS-related Kaposi's sarcoma cases. Not known whether α-interferon has anti-HIV activity in vivo.

Interleukin-2 (IL-2). Protein made by white blood cells that mediates production of interferon. Inability to produce IL-2 may predispose AIDS patients to opportunistic infections. Preliminary results of therapy with recombinant IL-2 not encouraging, but trials continue.

D-Penicillamine (3-mercapto-D-valine). Used to treat rheumatoid arthritis and Wilson's disease, a rare copper-storage disease. Inhibits HIV reproduction in humans. In trials at George Washington University Medical Center, it suppressed the virus but also temporarily depressed T cell levels in 13 AIDS patients with perpetually swollen glands.

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). Synthetic nucleoside used to treat a viral respiratory infection in children. In early clinical trials, it inhibited viral replication and improved immune function in AIDS patients. Longer (24-week) trial in 373 ARC patients was completed last month; at 12 weeks, ribavirin's safety profile was judged to be acceptable, and the drug was found to be well tolerated. Final results will be available soon.

Suramin ($C_{51}H_{34}N_6Na_6O_{23}S_6$). Antiparasitic agent. Potent inhibitor of HIV reverse transcriptase, but also significantly inhibits desirable biological functions. In AIDS patients, it has produced little or no evidence of clinical improvement or immunologic recovery. Has serious side effects, inability to penetrate central nervous system. Not considered appropriate for single-agent use in AIDS. No longer being actively pursued.

some and transcribed into RNA. Following a complicated series of events, the new RNA is encapsulated inside a newly constructed virus shell. The virus particle thus created buds from the host cell and can proceed to infect a new cell.

These processes are controlled by HIV's genes, of which there are at least seven. Each of the genes, and the protein products whose production they control, could serve as a specific target for new therapeutic strategies, says Samuel Broder, who directs clinical research at NCI. Broder's research group, for instance, is exploring the possibility of inhibiting the *tat*-III gene or the *trs* (also known as *art*) gene. These two genes make regulatory—as opposed to structural—proteins, and if they could be "knocked out," the virus might not be able to reproduce.

AZT and most of the other compounds presently being touted as potential weapons against AIDS were picked out initially because they were shown to inhibit replication of the virus in vitro. Many of these compounds are thought to do this by interfering with reverse transcriptase, a key viral enzyme in the replication process. This enzyme builds a DNA copy of the virus's RNA genome using thymidine triphosphate and other nucleotide building blocks found in the host cell. AZT can bollix this process, presumably, because reverse transcriptase mistakes AZT triphosphate for thymidine triphosphate and incorporates the azido derivative in the growing DNA chain. Then, when the enzyme attempts to append the next nucleotide, it is stymied because the necessary 3'-hydroxy group on the "ersatz thymidine" (AZT) is missing. The chain is thus terminated, and so is the virus's replication.

Researchers have synthesized other "false building blocks"—some of them structurally very similar to AZT—that they believe may be more potent and less toxic than AZT. For example, NCI has just begun testing 2',3'-dideoxycytidine in patients with AIDS or a milder form of the disease known as AIDS-related complex (ARC). Dideoxycytidine is "the most potent drug we've found so far," Broder says. Another nucleoside analog, 2',3'-dideoxyadenosine, also is being given high priority as a potential anti-AIDS agent by government scientists.

Ribavirin, a triazole nucleoside that has been pitted against more kinds of viruses than any other antiviral agent, also shows promising activity in AIDS patients. In a short-term clinical trial, ribavirin inhibited HIV replication and enhanced the immune system. More-extensive clinical trials to test the drug's safety and efficacy have now been completed and results are expected soon.

At the University of Georgia, chemist Chung K. Chu has synthesized some 60 nucleoside analogs related to AZT as part of a drug discovery effort led by Raymond F. Schinazi, a viral pharmacologist at the Veterans Administration Medical Center and Emory University, both in Atlanta. One of their most promising candidates is 3'-azido-2',3'-dideoxy-5-ethyluridine, code-named CS-85. Structurally, it differs from AZT only in that the pyrimidine ring has an ethyl group instead of a methyl at the 5-position. CS-85 inhibits viral replication and, when tested in human bone

marrow cells, was found to be much less toxic than AZT. CS-85 hasn't yet been tested in humans.

One limitation of CS-85 is that it doesn't prevent HIV-infected cells from binding to healthy cells. This fusion process depletes the immune system of important cells called T4 lymphocytes. Schinazi has found that several members of a class of inorganic compounds called heteropolytungstates can prevent fusion in cultured cells that are already infected. One example is silicotungstic acid, $H_4[SiO_4 \cdot (W_3O_9)_4]$, an industrial chemical that Emory University chemist Craig L. Hill made for Schinazi in highly purified form. This and other heteropolytungstates are "essentially nontoxic" in cell culture, Schinazi says, and he hopes to begin examining their effects in monkeys soon. They may turn out to be an improvement over HPA-23, an antimoniotungstate that has produced mixed results in AIDS patients.

Other potential anti-HIV drugs now being studied operate via still other mechanisms, the majority of which are not completely understood. For instance, a mayonnaiselike mixture of lipids called AL 721 appears to kill the AIDS virus by disrupting its protein membrane. And recombinant α-interferon seems to make cells resistant to infection by HIV.

But whatever its mechanism of action, an effective antiviral must be able to penetrate the blood-brain barrier. This capability is particularly important for treating patients with advanced cases of AIDS, because HIV is known to seek sanctuary in the brain of such patients.

Besides antiviral agents, scientists also are evaluating a variety of immune modulators that might be able to reinvigorate the AIDS patient's weakened defenses against infections. Some immune modulators, like ampligen and interleukin-2, mediate the body's own production of interferons (glycoproteins important in the immune response). Others, like isoprinosine and α-interferon, appear to have both immunostimulatory and antiviral activity, at least in vitro.

Several immune modulators have shown some promise in treating specific opportunistic infections. In one early trial of α-interferon, for example, a number of AIDS patients with Kaposi's sarcoma (a cancer that originates in blood-vessel walls) achieved complete remission, even though the researchers saw no signs of immune enhancement.

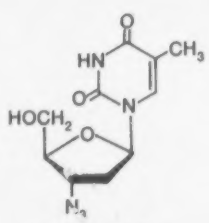
Researchers also have been trying to restore the immune system using more direct means. In the most successful approach so far, an AIDS patient who received bone-marrow transplants from his identical twin brother 15 months ago continues to improve, according to NIAID director Anthony S. Fauci. But whether this strategy can correct the underlying immune defect permanently is unknown.

Because the vast majority of persons infected with HIV presently show no clinical signs of AIDS-related infections or malignancies, there obviously is a need for antiviral drugs that will prevent these individuals from developing ARC or full-blown AIDS. But the testing of experimental drugs in those infected yet healthy persons could pose major practical and ethical problems because the drugs could be potentially dangerous. Furthermore, evaluating whether a candidate drug has protective effects would require volunteers to be monitored for years. That's because HIV has the cunning ability to remain latent in its host for long periods of time before it starts its devastating rampage through the immune system. Scientists don't understand what causes the virus to arise from its dormancy. Until they do, they have little chance of developing chemotherapy to eliminate the virus.

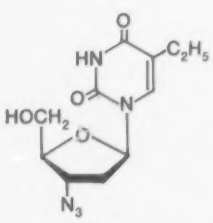
If a drug is developed that limits—but does not eliminate—expression of the virus, lifelong therapy may be necessary to protect infected persons. And "if lifelong therapy is required, the already difficult challenge of devising drugs of acceptable toxicity will prove even more severe," warns a book-length report on AIDS issued last month by the Institute of Medicine and the National Academy of Sciences (C&EN, Nov. 3, page 4).

Because of HIV's ability to hibernate in the body, it may not be possible to root it out. Antiviral drugs

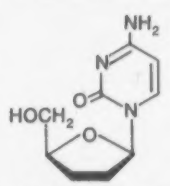
Some experimental anti-AIDS drugs have relatively simple structures



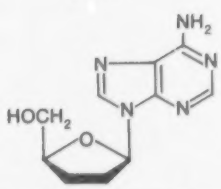
Azidothymidine



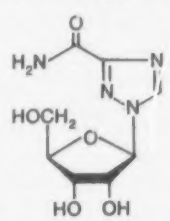
CS-85



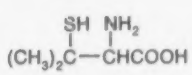
2',3'-Dideoxycytidine



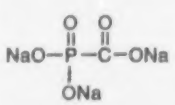
2',3'-Dideoxyadenosine



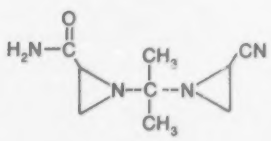
Ribavirin



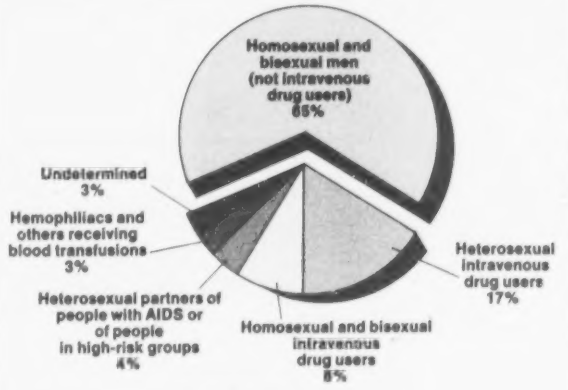
D-Penicillamine



Foscarnet



Azimexon


Most AIDS cases are sexually transmitted
Homosexual and bisexual men (not intravenous drug users) 65%
Undetermined 3%
Hemophiliacs and others receiving blood transfusions 3%
Heterosexual partners of people with AIDS or of people in high-risk groups 4%
Homosexual and bisexual intravenous drug users 5%
Heterosexual intravenous drug users 17%
Total cases = 26,199*
* Adult and adolescent cases in U.S., reported between 1981 and Oct. 20, 1986.
Source: Centers for Disease Control

might be able to keep the virus in check, but they probably won't be able to cure the disease.

Therefore, the most promising way to deal with the deadly threat of HIV is to prevent infection in the first place. Scientists only recently have begun to search for a vaccine against AIDS. And if their track record for producing vaccines against other animal retroviruses is any indication, their current quest will be slow and fraught with difficulties. In fact, some researchers even question whether an effective AIDS vaccine is possible.

A vaccine against AIDS might be derived from a harmless variant of the disease-causing agent, HIV. Such a variant would contain an antigen, or protein that triggers the immune system to produce neutralizing antibodies—specialized proteins that recognize and attack HIV particles if they enter the body later.

But it's not that simple. HIV is an immensely formidable foe because it uses "every biological trick in the book," says biotechnology consultant Heil. For example, according to a recent report on AIDS from Johns Hopkins University, "although some persons naturally produce antibodies to HIV that are weakly protective, these antibodies generally do not destroy the virus." However, the report goes on to say, "This does not necessarily mean that vaccine-induced antibodies will not destroy the virus [because] they may be quite different from those induced by the natural virus."

A related problem is the disquieting possibility that the AIDS virus can sneak into the body stowed away inside cells found in blood and semen, Emory's Schinazi says. Such infected cells then could fuse with healthy T lymphocytes, undermining the immune response and creating virus factories in the same blow. No one can say whether a vaccine would be effective against this cell-to-cell route of transmission.

A further difficulty confounding vaccine developers is the virus's genetic variability. Numerous strains of HIV are known, and the protein structure of each of these variants is significantly different, especially in the virus's outer coat (envelope), which is the part usually recognized and attacked by antibodies. New HIV strains are continually appearing because the virus mutates rapidly. Therefore, a vaccine derived from the envelope of one strain might not protect against other strains because the antibodies it induces might not recognize them.

In trying to block infection by the AIDS virus, researchers are exploring many avenues. One of these involves identifying the viral proteins or protein fragments that will elicit a protective immune response. This might be accomplished, for example, by isolating protein from HIV or chemically synthesizing peptide fragments of an HIV protein. Because of HIV's genetic variability, researchers are examining different strains of the virus, hoping to identify the envelope proteins that remain constant. These antigenic proteins possibly could serve as subunits for a vaccine that would be effective against a variety of strains.

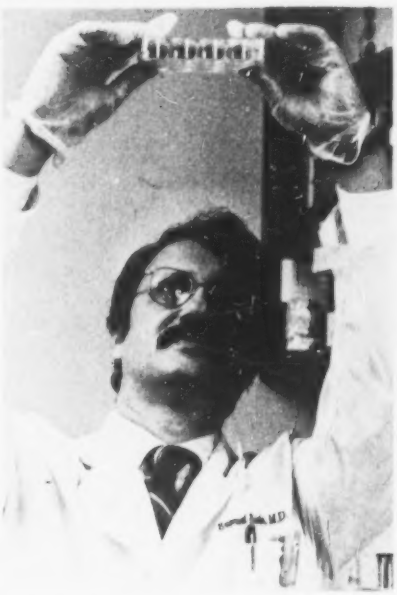
It might also be possible to develop a vaccine that would induce antibodies to attack the inner-core (*gag*) proteins of HIV, which apparently vary less than the envelope proteins. Researchers Prem S. Sarin of NCI, Allan L. Goldstein of George Washington University school of medicine, and their coworkers recently found that antibodies to a synthetic version of a natural human thymic hormone called thymosin α_1 attack the *gag* protein, neutralizing HIV in vitro. This occurs because the *gag* protein resembles thymosin in certain amino acid sequences. Thus, a vaccine based on thymosin, the *gag* protein, or synthetic peptides resembling their homologous region might immunize people successfully.

Antigenic viral proteins also can be produced using genetic engineering techniques. Recently, for example, Laurence A. Lasky, Phillip W. Berman, and their coworkers at Genentech in South San Francisco induced a mammalian cell line to make an HIV envelope glycoprotein that elicited antibodies in rabbits and guinea pigs. Some of these antibodies were shown to inactivate the AIDS virus in vitro by Jerome E. Groopman's group at New England Deaconess Hospital in Boston. Genentech researchers are believed to be testing the glycoprotein in chimpanzees to see if the animals produce neutralizing antibodies. If they do, they will be challenged with the AIDS virus to see if they are protected from infection.

Another recombinant approach to a vaccine was reported recently by two independent research groups. They spliced the envelope gene *env* of HIV into the vaccinia virus, which forms the basis of the smallpox vaccine. One group, led by Shiu-Lok Hu of Oncogen in Seattle, showed that macaque monkeys injected with this recombinant virus not only produced antibodies to HIV envelope proteins but triggered T lymphocytes to mount a cellular immune response (C&EN, Sept. 29, page 6). Hu's team is studying the vaccine in chimpanzees to see whether it protects against the virus.

The other group, consisting of Bernard Moss of NIAID and his colleagues there and at NCI, treated

NCI photo



NCI's Broder (left) and Emory University's Schinazi are studying antiviral activity of nucleoside analogs and other potential drugs

C&EN staff photo

monkeys with a similarly altered vaccinia virus, removed their cells, and exposed these to live AIDS virus in vitro. The cells did not become infected.

Although these results are encouraging, vaccinia virus has at least one major drawback: It could cause serious infection if given to a person whose immune system is already compromised.

Scientists also are considering the possibility that a naturally occurring, nonpathogenic relative of HIV might serve as the basis of an AIDS vaccine. Earlier this year, an international team of researchers led by virologist Myron E. Essex of the Harvard School of Public Health reported finding a new virus in healthy female prostitutes in Senegal. The new virus is genetically similar to HIV and is called HTLV-IV, that is, the fourth member of the human T-cell lymphotropic virus family, of which HIV also is a member.

HTLV-IV, which has infected people in western Africa for years, induces neutralizing antibodies to AIDS. So far, though, it does not seem to have caused the disease itself. Essex's group is examining the possibility that persons infected with HTLV-IV are protected from subsequent infection with HIV. "There may be a vaccine lead in this direction," Heil comments, "but you would have to be dead certain that HTLV-IV doesn't cause AIDS."

Essex's approach may have some allure because live-virus vaccines have tended to elicit a better immune response than vaccines based on killed virus, viral fragments, or other proteins.

But in the case of AIDS, most researchers are wary of using a live virus as a vaccine, according to molecular biologist Joseph G. Sodroski of Harvard's Dana-Farber Cancer Institute in Boston. "No one's going to inject a live retrovirus into healthy people," he says. "Even if it couldn't cause AIDS, there would be no way to guarantee that it wouldn't cause malignancy in 10 or 15 years."

Similarly, the use of killed HIV as an AIDS vaccine is suspect because of fears the virus might revitalize itself.

In their quest for an AIDS vaccine, scientists are having to contend with several research-related obstacles. The most basic one, of course, is their limited understanding of the immune response to HIV infection. Another is the scarcity of chimpanzees, which are needed to test the safety and efficacy of experimental HIV vaccines before clinical trials. Chimpanzees have been declared an endangered species; only about 1400 are now available for all biomedical research, according to NAS. As important as chimps are, though, they are deficient as an animal model for studying AIDS infection and disease, and that, too, has slowed vaccine development, notes NCI researcher Robert C. Gallo.

Assuming a vaccine does emerge from animal tests, the human testing will pose practical and ethical problems. For example, testing an HIV vaccine in uninfected volunteers would seem to require that some of them engage in high-risk activities so as to expose themselves to the deadly virus. In addition, a vaccine's side effects might discourage healthy, high-risk individuals from volunteering for trials.

Economic and legal considerations also are retarding vaccine research. Large pharmaceutical firms are reluctant to commit to vaccine development because such programs tend to be extremely expensive and traditionally have not provided a high return on investment capital. Pharmaceutical companies also are concerned that they would be sued for any vaccine-related injuries.

In light of these realities and uncertainties, no one expects an AIDS vaccine to become available before the early 1990s.

Nevertheless, Harvard's Essex predicts that vaccine development will see "dramatic progress" within the next two to three years. "Certainly within a year we'll have a much better idea of the feasibility for success," he says.

For now, though, the best preventative is education, according to U.S. Surgeon General C. Everett Koop and other public health officials. Their most basic message is that every adult and adolescent must be made aware that they can virtually eliminate their risk of infection by following two guidelines:

- Use a condom during sexual intercourse—either anal or vaginal—with someone who might be infected.
- Avoid illegal intravenous drugs, or at the very least, don't share needles and syringes.

That message, public health experts say, must be spread to all corners of society if society is to survive the specter of AIDS. □

Pharmaceutical Earnings Remain High

Earnings at major U.S. pharmaceutical companies continued their strong advances in the third quarter, but profit margins fell on average, as sales gains outpaced those for profits.

For 14 major drug-producing firms, after-tax earnings, excluding extraordinary and nonrecurring items, rose an average of 14% from last year's third quarter to a total of $1.42 billion. Sales for the group increased 21% to $11.5 billion. The group's average profit margin (after-tax earnings as a percentage of sales) dropped to 12.3% from 13.1% in the third quarter of 1985.

As in the second quarter, companies credited increased foreign sales brought about by the weaker dollar for much of the improvement. For instance, at Schering-Plough, Robert P. Luciano, chairman and chief executive officer, says the company's third-quarter results reflect an "exceptional" 32% increase in worldwide pharmaceutical sales. Luciano says the international pharmaceutical business continued to show a strong sales increase, both as reported in dollars and as measured in local currencies. Schering-Plough had an earnings increase of 42% to $62.3 million for the quarter on a sales rise of 19% to $601 million.

For Upjohn, whose sales increased 18% to $561 million and earnings rose 33% to $60.6 million, foreign sales increased 20% to $197 million and amounted to 35% of the company's consolidated sales.

Edmund T. Pratt Jr., chairman and chief executive officer of Pfizer, says the weaker dollar had a favorable impact on his company's reported results. "The effect of currency translation improved worldwide sales growth from 8% to 15% in the third quarter and from 6% to 12% for the first nine months of 1986," he says. Pfizer's earnings in the third quarter rose 14% to $177 million on that 15% sales increase to $1.16 billion.

Sterling Drug, which had a 14% rise in earnings to $51.3 million and a 20% increase in sales to $558 million, says the substantial sales gain for Sterling International, which encompasses all of the company's businesses abroad, was led by significant increases in Europe and Canada. But the favorable effect of the weakening of the dollar against major European currencies was largely offset by unfavorable currency effects in other parts of the world.

Productivity also played its share in improving earnings for the quarter. At Merck, whose earnings rose 27% to $173 million on a sales gain of 23% to $1.05 billion, chairman and chief executive officer P. Roy Vagelos says, "Income gains and improved earnings margins resulted from a better product mix and the continuation of cost controls and productivity improvements." He also credits the weaker dollar.

One company on the list—Baxter Travenol—recorded a 167% sales growth in the quarter to $1.38 billion. This was due to the company's acquisition of American Hospital Products in late 1985. The firm's earnings growth was a more normal 20% to $49 million.

For the first nine months of this year, the 14 companies had an average earnings growth of 14% to a combined $4.06 billion on a 19% sales increase to $33.6 billion. Profitability averaged 12.1% in the first three quarters this year compared with 12.7% in the comparable period last year.

William Storck, New York

Third-quarter earnings up sharply at many pharmaceutical companies

	THIRD-QUARTER 1986						NINE-MONTHS 1986					
	Sales	Earnings[a]	Change from 1985		Profit margin[b]		Sales	Earnings[a]	Change from 1985		Profit margin[b]	
	($ millions)		Sales	Earnings	1986	1985	($ millions)		Sales	Earnings	1986	1985
American Home Products	$1271.0	$201.3	5%	−2%	15.8%	17.0%	$3733.7	$579.5	6%	9%	15.5%	15.1%
Baxter Travenol	1382.0	49.0	167	20	3.5	7.9	4108.0	122.0	171	6	3.0	7.6
Becton Dickinson	389.6	31.5	23	9	8.1	9.1	1311.6	111.9	15	27	8.5	7.7
Bristol-Myers	1264.6	173.9	8	20	13.8	12.3	3630.3	437.8	9	12	12.1	11.7
Lilly	883.4	135.6	12	11	15.3	15.5	2751.0	433.9	12	10	15.8	16.0
Merck	1053.7	173.0	23	27	16.4	15.9	2979.8	503.9	15	24	16.9	15.7
Pfizer	1163.1	176.6	15	14	15.2	15.4	3313.1	501.6	12	14	15.1	14.8
A. H. Robins	215.0	25.0	14	40	11.6	9.4	579.1	55.6	11	25	9.6	8.6
Schering-Plough	600.6	62.3	19	42	10.4	8.6	1798.6	205.9	16	31	11.4	10.2
SmithKline Beckman	956.4	134.0	17	2	14.0	16.0	2702.1	402.6	14	5	14.9	16.3
Squibb	462.8	78.5	31	26	17.0	17.7	1277.8	192.4	27	19	15.1	16.0
Sterling Drug	557.8	51.3	20	14	9.2	9.7	1466.8	123.2	14	12	8.4	8.6
Upjohn	561.2	60.6	18	33	10.8	9.6	1692.8	188.3	13	23	11.1	10.2
Warner-Lambert	782.2	67.3	−6	10	8.6	7.3	2290.3	205.0	−6	9	9.0	7.7

a Earnings from continuing operations excluding significant nonrecurring and extraordinary items. b After-tax earnings as a percentage of sales.